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# EFFECT OF SINGLE DOSE OF MINOCYCLINE ON A CHLOROQUINE RESISTANT FALCIPARUM INFECTION FROM BALIKPAPAN, KALIMANTAN.

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*Selain 3 kasus P. falciparum yang resistent terhadap chloroquine dari Samarinda (Verdrager & Arwati, 1974) baru-baru ini ditemukan lagi satu kasus juga dari Kalimantan Timur, tetapi dari daerah yang lain (Balikpapan).*

*Terhadap kasus yang terakhir ini dilaksanakan sensitivity test sesuai dengan standar WHO. Disamping test tersebut, kepada penderita diberikan pula sensitivity test dengan 300 mg minocycline secara single dose. Minocycline yang merupakan derivat dari tetracyclin mempunyai khasiat anti malaria. Pengobatan radical dapat dicapai (pada 9 penderita sukarela yang menderita malaria strain dari Vietnam) sesudah 7 hari pengobatan. Dengan pemberian 300 mg minocycline base secara single dose, bentuk asexual dari parasite menghilang untuk jangka waktu 2 minggu. Effek ini sama dengan effek pemberian 1.500 mg chloroquine base, hanya hilangnya parasit bentuk asexual lebih lambat.*

*Pemberian pengobatan dengan minocycline dengan jangka yang lebih lama sebagai yang dikemukakan oleh WHO (1975) mungkin dapat mengobati radikal strain P. falciparum yang resistent terhadap chloroquine.*

Resistance of *Plasmodium falciparum* to chloroquine (RI level) in Indonesia has recently been reported in three patients from Samarinda, Kalimantan (Verdrager & Arwati, 1974). Another resistant *P. falciparum* case from the same Province, East Kalimantan, but from another area, Balikpapan, has been detected more recently.

This infection was also resistant to chloroquine at the RI level. A single dose treatment using 300 mg minocycline resulted in the disappearance of the asexual forms for a period of 2 weeks, similar to the one following the administration of 1500 mg chloroquine base. The infection was terminated by a single dose of the combination of 1 g sulfadoxine and 50 mg pyrimethamine.

The patient F.X. Sukardi, aged 24, a geology student from the "Technical Academy" of Yogyakarta was sent to Kalimantan for practical training with Pertamina (National Oil Company of Indonesia). He left Jakarta by plane on 10 July 1973 for Balikpapan where he stayed until 19 July. From there he was sent by helicopter to Mantoko (20–31 July), Sangata (1–6 August) and Pinang (7 August – 14 October).

All these places are Pertamina camps located in the forest. Mantoko and Pinang are flying camps where the staff sleep practically in the open. The student and other staff were provided with chloroquine tablets, the recommended dose being 2 tablets every day.

After his return to Balikpapan on 15 October the patient stopped taking chloroquine. On 24 October he started to be sick with fever. On 27 October a blood smear was taken but said to be negative. However on 30 October after another slide was taken, the diagnosis of malaria was made and the patient hospitalized in Pertamina hospital where he received a 3 day course of chloroquine. He was released on 7 November but on 16 November was again positive and given a second radical treatment.

On 19 December the patient returned to Jakarta by plane and reached Yogyakarta on 21 December. The following day a thick film was

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taken by the malaria section and found positive for *P. falciparum* (rings and gametocytes). In Yogyakarta he had a further four recrudescences after "radical treatment" with either chloroquine or amodiaquine (table 1). No other cases were detected in his village during this period or in 1973. Contacts were negative. On 24 April during the latest recrudescence the patient was sent to Jakarta where heparinized blood samples were collected on 25 and 26 April 1974. T heparinized blood was then glycerolized a frozen at −60°C and kept in the NAMR research unit laboratory to be handed over Dr. D.F. Clyde, University of Maryland Scho of Medicine, for subinoculation into voluntee

At the time of collection the parasite densi (asexual forms) was 2200 per mm3. Serum w also collected for Australian antigen testing.

Table 1 Summary of treatments given to patient Sukardi (in Yogyakarta)

| Date | Parasites | Drug doses (in mg base) | | | | | Remarks |
|---|---|---|---|---|---|---|---|
| | | amodia-quine | chloro-quine | pyrime-thamine | prima-quine | duration | |
| 22 Dec. 73 | F+ Fg+ | | 300 | 50 | | single dose | |
| 7–9 Jan. 74 | | *1500* | | | 45 | 3 days | |
| 24 Jan. | F++ | | 300 | 50 | | single dose | |
| 26–28 Jan. | | *1500* | | | 45 | 3 days | vomiting reported 2 hours after 1st dose 4 hours after 2nd dose |
| 30 Jan. | Neg. | | | | | | |
| 7 Feb. | Neg. | | | | | | |
| 14 Feb. | F+++ | | 450 | 50 | | single dose | |
| 15–17 Feb. | | | *1500* | | 45 | 3 days | vomiting reported 7 hours after 2nd dose 9 hours after 3rd dose |
| 28 Feb. | Neg. | | | | | | |
| 8 March | F++ | | | | | | |
| 21–23 Mar. | | | *1500* | | 45 | 3 days | |
| 10 April | F+ | | 450 | 50 | | single dose | |
| 15–24 Apr. | F+ Fg+ | | | | | | |

amodiaquine : Camoquin, Parke-Davis, 150 mg base
chloroquine : Nivaquine, Specia, 150 mg base
pyrimethamine : Daraprim, Burroughs-Wellcome, 25 mg
Malocide, Specia, 25 mg

## MATERIALS AND METHODS

*Sensitivity test to a standard dose of chloroquine.*

On his return to Yogyakarta a test for strain sensitivity to a standard dose of 1500 mg base chloroquine was carried out. On 30 April, the patient with an already very low asexual parasitaemia (he was positive since 10 April and received 75 mg of pyrimethamine on 26 April was given chloroquine 1.5 g (base) over a day-period. Asexual parasitaemia rapidly cleare to reappear three weeks later (on day 18 of th test). Belladonna tablets were given to preven possible vomiting which were previously re ported by the patient. Urine test was carrie out using Mayer Tanret reagent. Results ar summarized in table 2 and illustrated in fig. I & II

Table 2 Results of test for P. falciparum strain sensitivity to a standard dose of chloroquine in patient SUKARDI

Name F.X. Sukardi
Age 24 Sex male Weight (kg) 55
Condition asymptomatic
Blood count WBC 7500 RBC 3 680 000
Locality Desa Gilangharjo, Kampung Krekah, Bantul Regency
Origin Imported from Balikpapan area of East Kalimantan
Date of first administration of chloroquine (day 0) 30 April 1974
Particulars of chloroquine tablets chloroquine phosphate
Brand and Origin Resochin, Bayer samples
Dose of base per tablets : 150 mg

| Date | Day | P falciparum | | | | Drug, dose mg base | Urine test (Mayer-Tanret | Remarks |
|---|---|---|---|---|---|---|---|---|
| | | trophozoites | | gametocytes | | | | |
| | | count* | per mm3 | count* | per mm3 | | | |
| 23 Apr | −7 | 46 | 3450 | 2 | 150 | | | |
| 24 ,, | −6 | 50 | 3750 | 2 | 150 | | | |
| 25 ,, | −5 | | | | | | | IV blood collected |
| 26 ,, | −4 | 31 | 2325 | 3 | 225 | pyrimethamine, 75 | | IV blood collected |
| 27 ,, | −3 | 36 | 2700 | 4 | 300 | | | |
| 28 ,, | −2 | | | | | | | |
| 29 ,, | −1 | 16 | 1200 | 2 | 150 | | | |
| 30 ,, | 0 | 2 | 150 | 2 | 150 | *chloroquine*, 600 | − | with belladonna |
| 1 May | 1 | 3 | 225 | 5 | 375 | *chloroquine*, 600 | ++ | ,, ,, |
| 2 ,, | 2 | 0 | 0 | 3 | 225 | *chloroquine*, 300 | ++ | ,, ,, |
| 3 ,, | 3 | 0 | 0 | 2 | 150 | primaquine, 45 | ++ | |
| 4 ,, | 4 | 0 | 0 | 3 | 225 | | | |
| 5 ,, | 5 | 0 | 0 | 3 | 225 | | | |
| 6 ,, | 6 | 0 | 0 | 1 | 75 | | | |
| 7 ,, | 7 | 0 | 0 | 0 | 0 | | | |
| 8 ,, | 8 | 0 | 0 | 1/500 | 15 | | | |
| 9 ,, | 9 | 0 | 0 | 0 | 0 | | | |
| 10 ,, | 10 | 0 | 0 | 0 | 0 | | | |
| 11 ,, | 11 | | | | | | | |
| 12 ,, | 12 | 0 | 0 | 0 | 0 | | | |
| 13 ,, | 13 | | | | | | | |
| 14 ,, | 14 | 0 | 0 | 0 | 0 | | | |
| 15 ,, | 15 | | | | | | | |
| 16 ,, | 16 | 0 | 0 | 0 | 0 | | | |
| 17 ,, | 17 | | | | | | | |
| 18 ,, | 18 | 5 | 375 | 0 | 0 | | | |
| 19 ,, | 19 | | | | | | | |
| 20 ,, | 20 | 95 | 7125 | 0 | 0 | | | |
| 21 ,, | 21 | 25 | 1875 | 0 | 0 | | | |
| 22 ,, | 22 | 30 | 2250 | 0 | 0 | | | |
| 23 ,, | 23 | 24 | 1800 | 0 | 0 | | | |
| 24 ,, | 24 | 24 | 1800 | 0 | 0 | | | |
| 25 ,, | 25 | 27 | 2025 | 0 | 0 | | | |
| 26 ,, | 26 | 24 | 1800 | 1 only | < 1 | | | |
| 27 ,, | 27 | 25 | 1875 | 1/200 | 37 | | | |
| 28 ,, | 28 | | | | | | | |
| 29 ,, | 29 | 15 | 1125 | 10 | 750 | | | IV blood collected |
| 30 ,, | 0 | 13 | 975 | 15 | 1125 | *minocycline*, 300 | | single dose |
| 31 ,, | 1 | 14 | 1050 | 16 | 1200 | | | |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 | June | 2 | 17 | 1275 | 7 | 525 | primaquine, 45 |
| 2 | „ | 3 | 38 | 2850 | 9 | 675 | |
| 3 | „ | 4 | 0 | 0 | 2 | 150 | |
| 4 | „ | 5 | 0 | 0 | 1 | 75 | |
| 5 | „ | 6 | 0 | 0 | 0 | 0 | |
| 6 | „ | 7 | 0 | 0 | 0 | 0 | |
| 7 | „ | 8 | 0 | 0 | 0 | 0 | |
| 8 | „ | 9 | 0 | 0 | 0 | 0 | |
| 10 | „ | 11 | 0 | 0 | 0 | 0 | |
| 12 | „ | 13 | 0 | 0 | 0 | 0 | |
| 14 | „ | 15 | 0 | 0 | 0 | 0 | |
| 16 | „ | 17 | 0 | 0 | 0 | 0 | |
| 18 | „ | 19 | 1 | 75 | 0 | 0 | |
| 20 | „ | 21 | 10 | 750 | 0 | 0 | |
| 22 | „ | 23 | 150 | 11250 | 0 | 0 | |
| 24 | „ | 25 | 100 | 7500 | 0 | 0 | |
| 26 | „ | 27 | 11 | 825 | 1 only | <1 | |

* per 100 leucocytes.

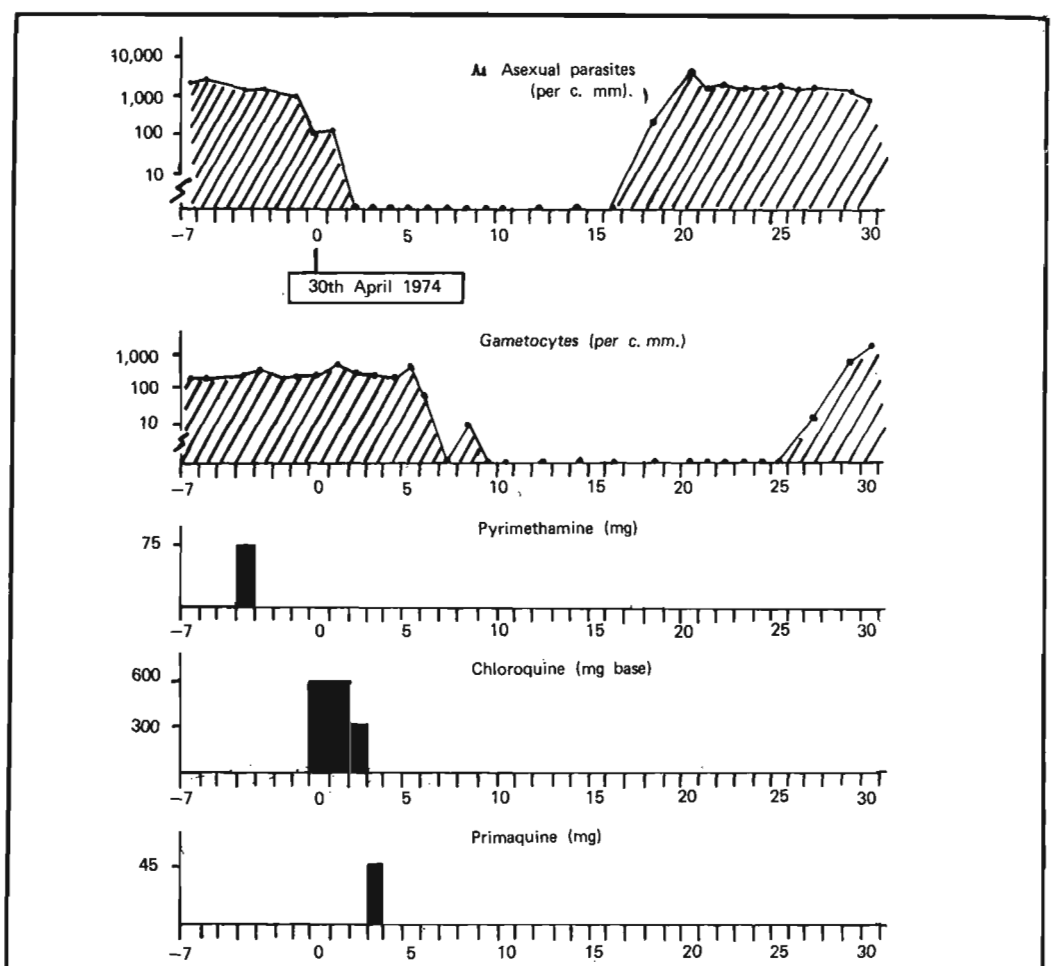


Fig. I Effect of Chloroquine, Pyrimethamine and Primaquine on a *P. falciparum* strain from BALIKPAPAN (KALIMANTAN).

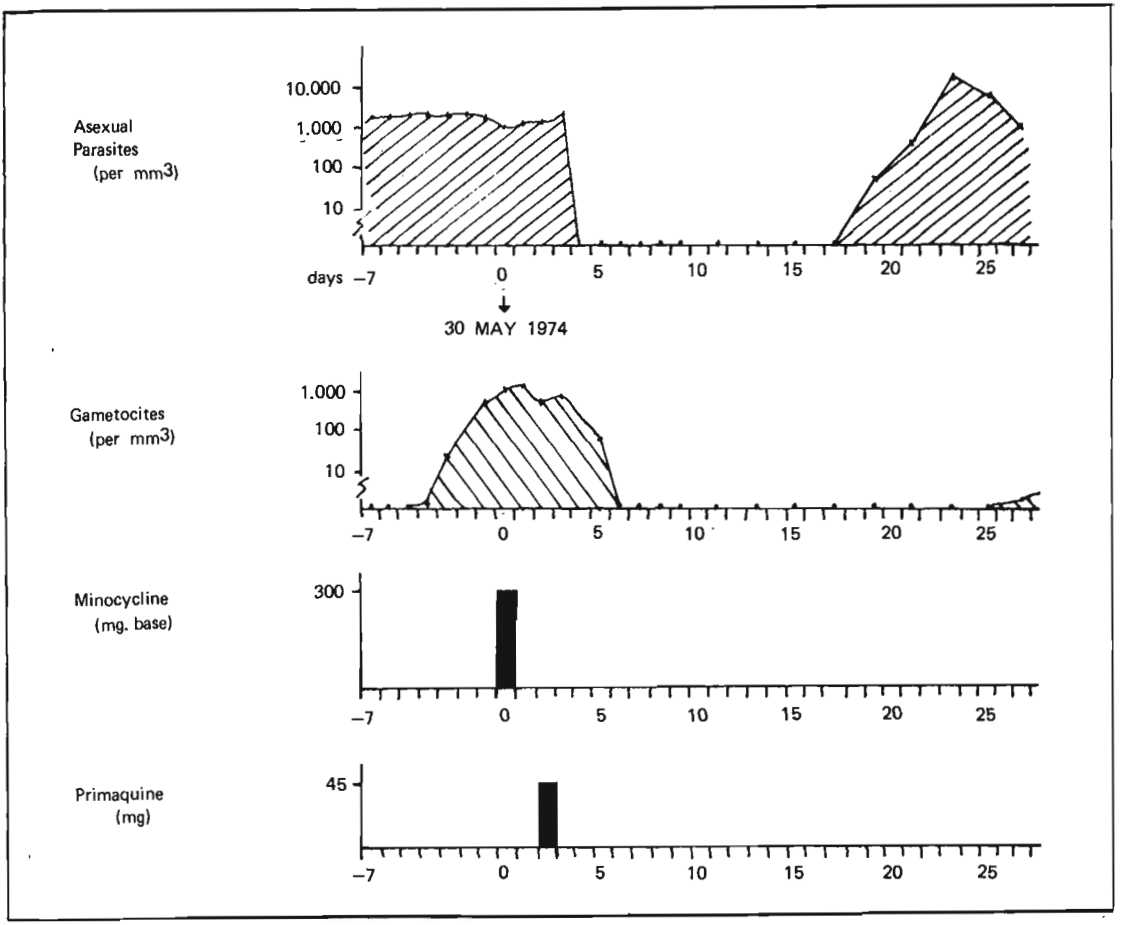


Fig. II Effect of Minocycline and Primaquine on a *P. falciparum* strain from BALIKPAPAN (KALIMANTAN).

*Sensitivity to a single dose of 300 mg minocycline base.*

Minocycline, a recently discovered derivative of tetracycline, has been shown to have antimalarial activity, Radical cure was obtained in 9 volunteers infected with the Vietnam (Marks) strain after 7 days of treatment; 5 men received 200 mg every 12 hours, 2 men received 200 mg once daily, and 2 men received 100 mg once daily (Willerson et al., 1972).

Similar dosages have been recommended by the manufacturer (Lederle) for the treatment of gonorrhoea. An alternative being a single dose of 300 mg base for gonococcal urethritis in males.

An attempt was therefore made to assess the effect of such a single dose in the treatment of the resistant *P. falciparum* infection.

## RESULTS

On 30 May 1974 the patient was given 300 mg of minocycline in a single dose. Asexual parasites increased progressively up to day 3, but then disappeared suddenly on day 4, to reappear on day 19. Details are given in table 2 and illustrated in fig II. The infection was terminated by administering a single dose of the combination of 1 g sulfadoxine and 50 mg pyrimethamine on 27 June 1974.

To summarize, the single dose of 300 mg minocycline base resulted in the disappearance of the asexual forms for a period of 2 weeks, similar to the one following the administration of 1500 mg chloroquine base but the disappearance of asexual parasitaemia was slower and the parasite count increased up to day 3. A longer minocycline treatment, as mentioned by

WHO (1973), may have achieved the radical cure of this chloroquine resistant *P. falciparum* infection.

## SUMMARY AND CONCLUSION

Another chloroquine resistant *P. falciparum* case (RI level) is reported from Kalimantan, formerly Borneo. The place of infection of this case in the Balikpapan area of East Kalimantan is very close to the Samarinda area where previous resistant cases were recently reported (Verdrager and Arwati, 1974).

The (RI) drug response to 4-aminoquinolines seems similar to the response of the Sabah (Kal.) strain reported by Clyde (1973). It is possible that this (Kal.) strain and similar chloroquine and pyrimethamine resistant strains are spreading south along the forest, carried by migrants and transmitted by *A.b. balabacensis* or other members of *A. leucosphyrus* group.

A single dose of 300 mg minocycline base resulted in the disappearance of the asexual parasites for a period of 2 weeks similar to the one following the administration of a 3-day course of 1500 mg chloroquine base but asexual parasitaemia was slower to disappear and the parasite count increased up to day 3. The infection was terminated by administering a single dose of the combination of 1 g sulfadoxine and 50 mg pyrimethamine.

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